Original Article

Adjuvant chemotherapy improves the prognosis of early stage resectable pulmonary large cell carcinoma: analysis of SEER data

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Background: Pulmonary large cell carcinoma (LCC) is a poorly differentiated and rare tumor with dismal outcome, and there are no recommended treatments for LCC. Little is known about the efficacy of post-operative chemotherapy in patients with early stage LCC.

Methods: The patients with early stage I/II LCC in the Surveillance, Epidemiology and End Results (SEER) database between 2004 and 2015 were retrospectively reviewed. The overall survival (OS) of patients with LCC at different stages and treatments were evaluated by Kaplan-Meier analysis with log-rank test. Univariate and multivariate Cox proportional risk regression analysis were employed to determine the independent risk factors of OS. Finally, a nomogram was constructed to predict the 1 -, 3- and 5-year OS of early stage LCC patients.

Results: A total of 1,099 pulmonary LCC cases were included in this study. 71.8% of patients were over 60 years old, and 66.7% of the tumor lesions located in the upper lobe, followed by the lower lobe (25.7%). Meanwhile, the majority of tumors showed poor differentiation (96.1%). The median OS of surgical patients with or without post-operative adjuvant chemotherapy was 61 and 47 months, respectively. Post-operative chemotherapy was associated with better OS (HR: 0.805; 95% CI: 0.676–0.959, P=0.020). For patients with tumor size >3 cm or IB stage tumor, the prognosis of postoperative chemotherapy was better than that of patients without chemotherapy. Multivariate Cox analysis revealed the age, stage and treatments were independent risk factors of OS for early stage LCC. The nomogram had a calibration index of 0.581.

Conclusions: The incidence of LCC was high in the elderly, and it generally had poor differentiation. Post-operative chemotherapy is strongly recommended for patients with LCC at stage IB or higher.

Keywords: Large cell carcinoma (LCC); adjuvant chemotherapy; SEER

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Introduction

Large cell carcinoma (LCC) is a rare subtype of non-small cell lung cancer (NSCLC), with an incidence of about 10% in NSCLC (1,2). According to the 2004 WHO lung cancer classification (3), LCC belongs to the undifferentiated cancer with poor prognosis and has five different variants. It has been reported that LCC mainly occurs in the elderly and is closely related to the cigarette smoking (4,5). Moreover, the diagnosis of LCC is largely dependent on post-operative pathological examination (6,7). In addition, currently, there is no recommended treatment for LCC, thus its treatments are often chosen according to the treatment experience of NSCLC. And it has

confirmed the survival benefits of adjuvant postoperative chemotherapy in stage II and IIIA NSCLC patients (8,9), but the value of adjuvant chemotherapy for stage IB in NSCLC remains controversial. In the Cancer and Leukemia Group B (CALGB) trial 9633, carboplatin-based adjuvant chemotherapy was found to have no influence on the prognosis of stage IB for NSCLC (10), which was also supported by the results of Park *et al.* (11) and Li *et al.* (12). Nevertheless, other studies had revealed opposite outcomes (13-15).

As a subtype of poor prognosis of NSCLC, the clinical characteristics, and treatments of early stage LCC are not well known. And the role of chemotherapy after surgery is still unclear in the early stage LCC. So in our study, the patients of LCC in the SEER database were retrospective reviewed, and the characteristics, prognosis, and survival of these patients were further analyzed.

Methods

Data extraction

Data of patients diagnosed with LCC between 2004 and 2015 were extracted using the SEER*Stat software version 8.3.5. The study cohort comprised patients who were diagnosed with LCC according to the International Classification of Disease for Oncology, the third edition (ICD-O-3) histology code 8012/3 (LCC, NOS), 8013/3 (large cell neuroendocrine carcinoma), and 8014/3 (LCC with rhabdoid phenotype). The large cell neuroendocrine carcinoma was also contained based on the 2004 WHO lung cancer classification (3). The exclusion criteria were as follows: (I) patients with more than one primary cancer; (II) patients diagnosed at stage III/IV; (III) patients without pathological confirmation based on histology; (IV) the clinical information was incomplete, including age, gender, race, marital status, primary site, laterality, grade, size, stage, chemotherapy, surgery and survival data. The TNM staging was reclassified for each patient based on the primary tumor size and tumor invasion according to the TNM classification for lung cancer (8^{th} Edition) (16) using R version 3.4.3 software. Approval was waived by the local ethics committee, as SEER data is publicly available and de-identified.

Overall survival (OS) refers to the interval from the date of diagnosis to the date of death or of the last follow-up. The survival time less than 1 month (encoded as zero in the SEER database) was assigned to 0.5 months according to the standard epidemiological convention.

Statistical analysis

Categorical variables were analyzed with the Pearson χ^2 test. The Kaplan-Meier method was used to estimate the survival probabilities with the log-rank test to assess any significant difference between OS stratified by each covariate. Cox proportional hazards model performed to assess the independent clinicopathological characteristics associated with the survival. Only the variables significantly related to the survival in univariate analysis were enrolled in multivariate analysis. Moreover, the nomogram was established based on the results of multivariate analysis by using R version 3.4.3 software. Prediction error was estimated with 1,000 bootstrap samples. A value of two-sided $P<0.05$ was considered statistically significant. Statistical analysis was conducted with SPSS version 25.0 (SPSS, Chicago, IL), and the GraphPad Prism 7 (GraphPad Software, San Diego, CA) was used to delineate the survival curve.

Results

Treatments of early-stage LCC

As shown in *Table 1*, a total of 1,099 patients with LCC were comprised in this study. 73.2% of patients underwent primary surgery alone, while the others received surgery with post-operative chemotherapy. Notably, 71.8% of patients were over 60 years old, and 66.7% of the lesions located in the upper lobe, followed by the lower lobe (25.7%). Most of tumors (96.1%) showed poor differentiation or undifferentiation. Furthermore, 64.1% of patients were diagnosed with LCC at stage I (IA: 38.3%; IB: 25.8%), and 35.9% at stage II. In addition, the age, tumor size, stage, and marital status were the factors related to the use of post-operative chemotherapy. Compared with patients with surgery alone, patients treated with adjuvant chemotherapy were younger ($P<0.001$), married cases ($P=0.013$), higher stage ($P<0.001$) and larger lesions ($P<0.001$).

OS of LCC patients

The median OS was 47 months (range, 0.5–143 months) in patients with surgery alone and 61 months (range, 0.5–142 months) in those with post-operative chemotherapy.

Table 1 Clinical characteristics of LCC patients with or without chemotherapy

Independent variables	ALL	Surgery	Surgery + chemotherapy	P value
Total	1,099	805 (73.2)	294 (26.8)	
Age (yr)				<0.001
≤60	310 (28.2)	186 (60.0)	124 (40.0)	
>60	789 (71.8)	619 (78.5)	170 (21.5)	
Gender				0.384
Female	521 (47.4)	388 (74.5)	133 (25.5)	
Male	578 (52.6)	417 (72.1)	161 (27.9)	
Race				0.293
White	945 (86)	691 (73.1)	254 (26.9)	
Black	104 (9.5)	73 (70.2)	31 (29.8)	
Other (American Indian/AK Native, Asian/Pacific Islander)	50 (4.5)	41 (82.0)	9 (18.0)	
Marital status				0.013
Married	628 (57.1)	440 (70.1)	188 (29.9)	
Single	118 (10.7)	87 (73.7)	31 (26.3)	
Separated/divorced/widowed	353 (32.1)	278 (78.8)	75 (21.2)	
Primary site				0.775
Main bronchus	7 (0.6)	5 (71.4)	2 (28.6)	
Upper lobe	733 (66.7)	530 (72.3)	203 (27.7)	
Middle lobe	59 (5.4)	42 (71.2)	17 (28.8)	
Lower lobe	282 (25.7)	214 (75.9)	68 (24.1)	
Overlapping lesion	10 (0.9)	7 (70.0)	3 (30.0)	
Lung, NOS	8 (0.7)	7 (87.5)	1 (12.5)	
Laterality				0.693
Left	478 (43.5)	353 (73.8)	125 (26.2)	
Right	621 (56.5)	452 (72.8)	169 (27.2)	
Grade				0.597
Well + moderate	43 (3.9)	33 (76.7)	10 (23.3)	
Poor + undifferentiated	1,056 (96.1)	772 (73.1)	284 (26.9)	
Size (cm)				<0.001
≤3	630 (57.3)	512 (81.3)	118 (18.7)	
3–7	469 (42.7)	293 (62.5)	176 (37.5)	
Stage				<0.001
IA	421 (38.3)	378 (89.8)	43 (10.2)	
IB	283 (25.8)	216 (76.3)	67 (23.7)	
II	395 (35.9)	211 (53.4)	184 (46.6)	

Data are n (%).

The cases with post-operative chemotherapy had a better OS than those with surgery alone (HR: 0.805; 95% CI: 0.676–0.959, P=0.020) (*Figure 1*). The 1-, 3-, 5-year survival rate for patients with combined chemotherapy was 85.7%, 60.6%, 50.7, separately, compared with 79.4%, 55.1% and 44.6% in cases with surgery alone.

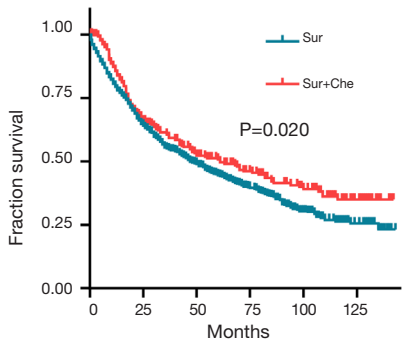

Figure 1 Kaplan-Meier analysis of OS of patients. OS, overall survival.

For the patients with tumor size ≤3 cm, there was no significant difference in the prognosis between patients with surgery alone and those with post-operative chemotherapy (HR: 0.918, 95% CI: 0.700–1.205, P=0.547) (*Figure 2A*). However, patients with post-operative chemotherapy had a better OS than those with surgery alone in patients with tumor size >3 cm (HR: 0.670, 95% CI: 0.528–0.851, P=0.002) (*Figure 2B*).

Meanwhile, the patients with stage IA LCC could not benefit from the post-operative chemotherapy in OS (HR: 0.966, 95% CI: 0.625–1.491, P=0.877, *Figure 3A*), but a significant difference was observed in OS between patients with or without post-operative chemotherapy in those with stage IB LCC (HR: 0.579, 95% CI: 0.411–0.815, P=0.006, *Figure 3B*) or stage II LCC (HR: 0.684, 95% CI: 0.529–0.883, P=0.004, *Figure 3C*).

The COX hazards regression analysis showed that age (P<0.001), stage (P=0.003) and treatments (P=0.021) were predictors of OS in univariate analysis (*Table 2*). All the covariates with P<0.1 in univariate analysis were included

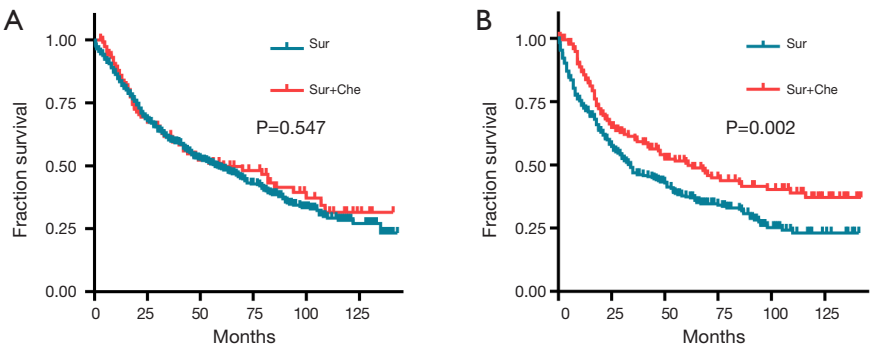

Figure 2 Kaplan-Meier estimate of OS of patients with (A) ≤3 cm, (B) 3–7 cm. OS, overall survival.

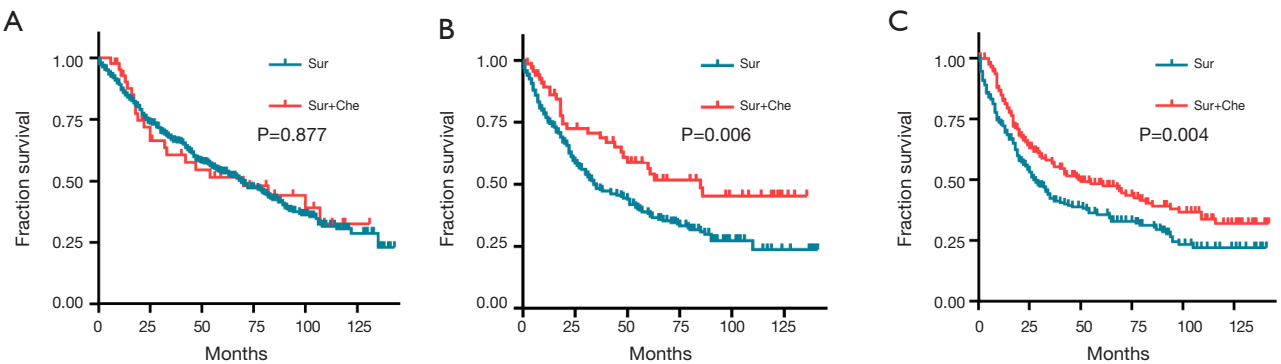

Figure 3 Kaplan-Meier estimate of OS of patients with (A) IA, (B) IB and (C) II. OS, overall survival.

Table 2 Univariate and multivariate Cox proportional hazard analyses of clinical characteristics for overall survival rates in patients with LCC

Independent variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (yr)		<0.001		0.001
≤60	1.00 (reference)		1.00 (reference)	
>60	1.418 (1.179–1.706)	<0.001	1.388 (1.150–1.677)	0.001
Gender		0.131		
Female	1.00 (reference)			
Male	1.128 (0.965–1.320)	0.131		
Race		0.669		
White	1.00 (reference)			
Black	0.888 (0.670–1.177)	0.41		
Other (American Indian/AK Native, Asian/Pacific Islander)	0.922 (0.622-1.367)	0.687		
Marital status		0.232		
Married	1.00 (reference)			
Single	1.062 (0.806–1.399)	0.67		
Separated/divorced/widowed	1.159 (0.979–1.372)	0.087		
Primary site		0.991		
Main bronchus	1.00 (reference)			
Upper lobe	1.203 (0.386–3.744)	0.75		
Middle lobe	1.157 (0.355–3.768)	0.809		
Lower lobe	1.23 (0.392–3.852)	0.723		
Overlapping lesion	0.964 (0.230–4.033)	0.96		
Lung, NOS	1.341 (0.320–5.613)	0.688		
Laterality		0.117		
Left	1.00 (reference)			
Right	0.882 (0.754–1.032)	0.117		
Grade		0.418		
Well + moderate	1.00 (reference)			
Poor + undifferentiated	0.853 (0.580–1.254)	0.418		
Size (cm)		0.066		<0.001
≤3	1.00 (reference)			
3–7	1.159 (0.990–1.356)	0.066		
Stage		0.003		<0.001
IA	1.00 (reference)		1.00 (reference)	
IB	1.271 (1.041–1.551)	0.018	1.324 (1.083–1.619)	0.006
II	1.351 (1.125–1.622)	0.001	1.568 (1.291–1.905)	0.001
Treatments		0.021		0.002
Surgery	1.00 (reference)		1.00 (reference)	
Surgery + chemotherapy	0.805 (0.669–0.968)	0.021	0.733 (0.600–0.895)	0.002

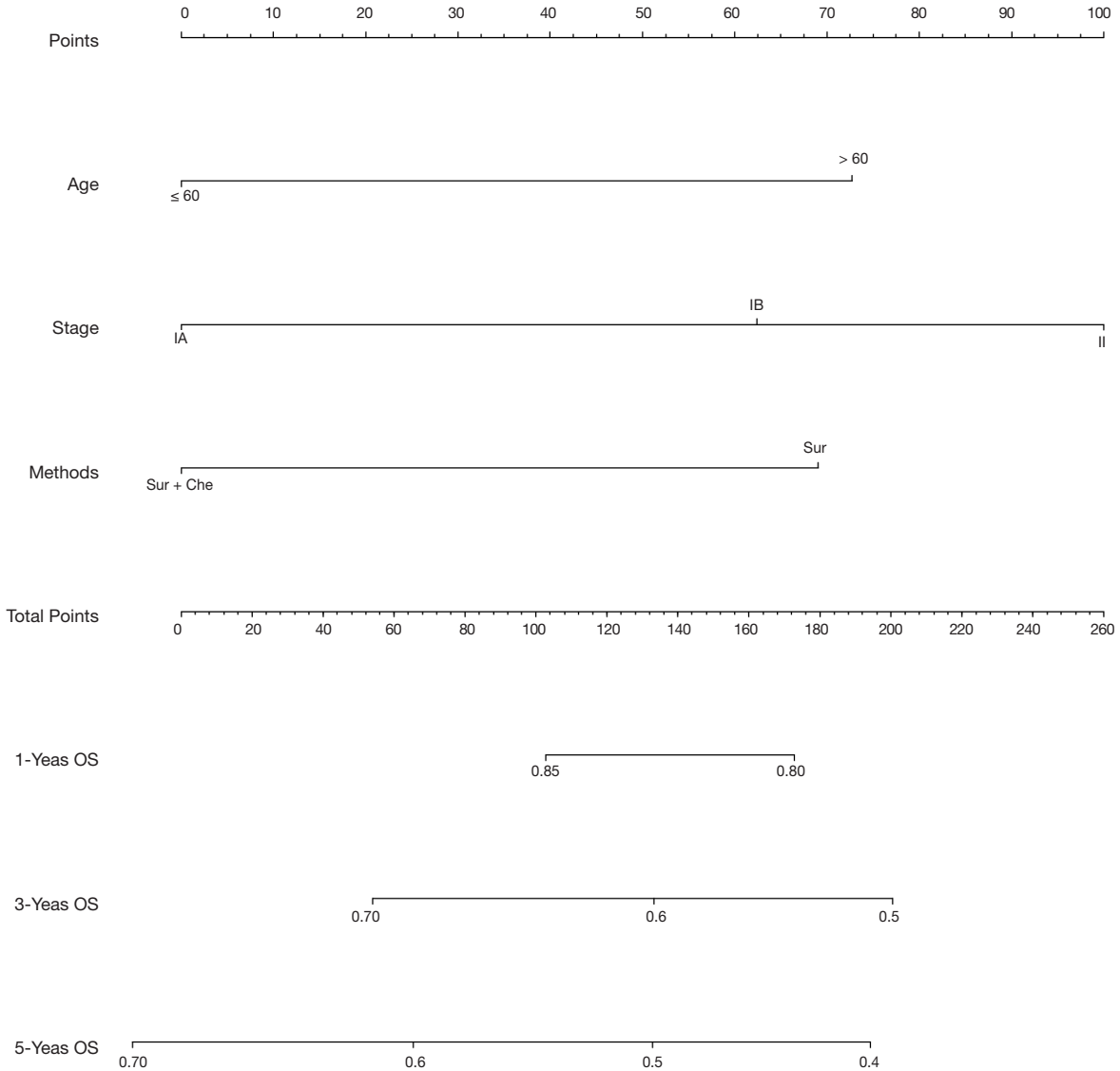

Figure 4 Nomogram to predict 1-, 3- and 5-year OS of patients with early stage LCC. OS, overall survival; LCC, large cell carcinoma.

into the multivariate analysis, and the results revealed that age (P=0.001), stage (P<0.001) and treatments (P=0.002) were independent factors to predict survival, which strongly suggested that post-operative chemotherapy was recommended for the patients with stage IB or II of LCC. A nomogram including the variables independently related to the survival was shown in *Figure 4*. The 1-, 3- and 5-year OS could be estimated by adding the points which are corresponding to the patient's characteristics. The C-index for the nomogram to predict OS was 0.581 (95% CI: 0.557–0.605). Calibration plots of the nomogram prediction accuracy were presented in *Figure 5*.

Discussion

Most LCC studies are case reports or have small sample size due to its rarity. Therefore, little is known about the clinical features and prognosis of LCC. In the present research, a total of 1,099 patients with stage I/II LCC were included and retrospectively analyzed.

It has been revealed that LCC mainly occurs in the elderly, and it is more common in males (1,5), which was consistent with our results. Sun *et al.* (17) had reported that the tumors mostly located in the left lung, which was contrary to our findings. This might be related to the small

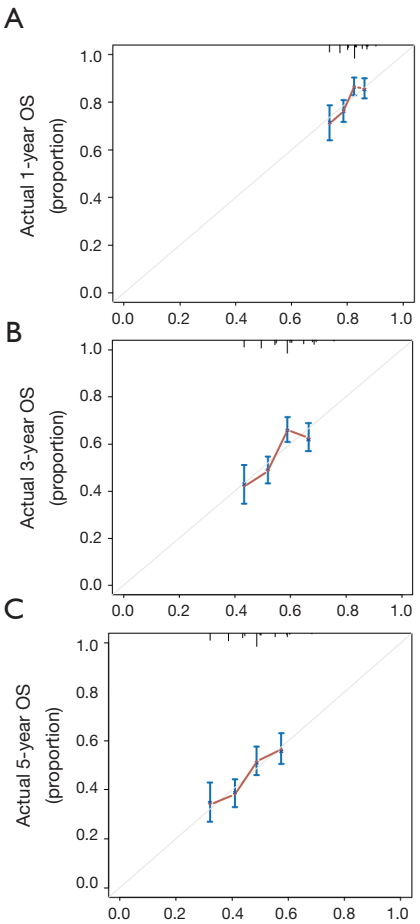

Figure 5 Calibration plots of the nomogram prediction of (A) 1-, (B) 3- and (C) 5-year OS of LCC patients. OS, overall survival; LCC, large cell carcinoma.

sample size in their study (n=46). Surprisingly, the primary LCC in most of the patients located in the upper lobe, followed by the lower lobe in our study.

Surgical resection is the first-line treatment for stage I or II NSCLC (5). In view of the unsatisfactory prognosis of LCC, for the early stage LCC, the surgical resection may not definitely achieve favorable prognosis. Gu *et al.* (18) and Lo Russo *et al.* (19) found that surgery combined with post-operative chemotherapy had a better prognosis compared to surgery alone for large cell neuroendocrine carcinoma, a subtype of LCC. Similarly, our study showed that the 5-year survival rate of LCC patients with surgery alone was 44.6%, while that was 50.7% in those with post-operative chemotherapy. Furthermore, our study also found no significant difference in the survival rate between patients with or without post-operative chemotherapy among patients with stage IA LCC (P=0.877). However, for patients with LCC at higher stage (IB or higher), the post-operative chemotherapy achieved a better OS than the surgery alone (P=0.006). This was consistent with the results reported by Raman *et al.* (20).

There are several limitations in this study. This was a retrospective study, and there was limited information on the treatments. Furthermore, the regimens of chemotherapy were unclear. However, this seems to have little effect on our analysis of the effects of postoperative chemotherapy or not.

Up to now, no peculiar or standard chemotherapy regimens for LCC were recommended in the guidelines of NSCLC treatment, and at which exact stage patients with early LCC should receive adjacent chemotherapy after surgery still lacks convincing clinical evidence. To the best of our knowledge, this research was the first and largest retrospective analysis of LCC to determine the efficacy of adjuvant chemotherapy after surgery in early pulmonary LCC. By our analysis, clinicians can better understand the clinicopathological characteristics, survival, and treatment of patients with early pulmonary LCC.

In conclusion, our study indicated that LCC has a higher incidence in the elderly and males, and tends to present poor differentiation. For early stage LCC, surgery combined with chemotherapy should be performed from stage IB, instead of stage II. However, more prospective studies are needed to confirm our findings.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Approval was waived by the local ethics committee, as SEER data is publicly available and de-identified.

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